On the influence of positive and negative feedback loops on the phase response curve of biological oscillators

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1 Introduction

Rhythmic phenomena are essential to the dynamic behavior of biological systems. They find their roots in the many regulatory mechanisms that control life at the cellular level. Understanding those molecular and cellular mechanisms is crucial to advances in systems biology.

Dynamic models of regulatory mechanisms are made of complex interconnections of feedback loops often described by bloc diagrams. In this research, our goal is to understand how entrainment and synchronization, two important system properties of biological oscillators, depend on the circuitry of these bloc diagrams. The general idea is illustrated on a particular model of cell mitosis [1].

2 Circuitry of oscillators

A single two-component negative feedback system can exhibit damped oscillations but will inevitably approach a stable steady state. Some aspect of the circuit must be altered to convert it into a sustained oscillator. Two basic types of bloc diagrams have been proposed for biological oscillators.

One type contains only negative feedback loop. With sufficient phase delay in the feedback loop, the system repeatedly overshoots and undershoots its steady state, leading to sustained oscillations [2, 3].

A second type of bloc diagrams contains both positive and negative feedback loops. The positive-feedback loop creates a bistable system (a toggle switch) and the negative-feedback loop drives the system back and forth between the two stable steady states [4, 5].

3 Infinitesimal phase response curve

The infinitesimal phase response curve (iPRC) has proven a very useful tool to study the input-output properties of oscillators. The start point is a dynamical system of the form

$$\dot{x} = f(x) + \varepsilon\, u(t), \quad x \in R^m, \tag{1}$$

having for $\varepsilon = 0$ a limit cycle attractor $\gamma \subset R^m$ with period T and frequency $\Omega = 2\pi/T$, and forced by a weak input $\varepsilon\, u(t)$.

Using an asymptotic method of reduction [6], the system (1) is transformed into the phase model

$$\dot{\theta} = \Omega + \varepsilon\, Q(\theta) \cdot u(t) \tag{2}$$

with $Q(\theta)$ being the iPRC. The iPRC tabulates the transient change in the cycle period of an oscillator induced by an infinitesimal perturbation as a function of the phase at which it is received.

The characterization of this phase model, especially its equilibria and their stability, is used to study the entrainment and the synchronization of the system. The shape of the iPRC plays thus a leading role in those properties.

4 Shaping the iPRC from the circuitry

We wish to relate the circuitry of the bloc diagram describing the biological oscillator and its iPRC. We illustrate this general question on a model of mitotic oscillations abundantly discussed in the literature [1].

References

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